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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/069,019	02/21/2002	Andrew Peter Thomas	056291-5011	1581
9629	7590	01/14/2004	EXAMINER	
MORGAN LEWIS & BOCKIUS LLP 1111 PENNSYLVANIA AVENUE NW WASHINGTON, DC 20004			BALASUBRAMANIAN, VENKATARAMAN	
			ART UNIT	PAPER NUMBER
			1624	11

DATE MAILED: 01/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/069,019

Applicant(s)

THOMAS ET AL.

Examiner

Venkataraman Balasubramanian

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 January 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-10 and 13-17 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-10 and 13-17 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6, 7, 9, 10. 6) ☐ Other: _____

DETAILED ACTION

Applicants' response, which included cancellation of claims 11-12, amendment to claims 3-7 and addition of new claims 13-17 are made of record.

Claims 1-10 and 13-17 are now pending.

In view of applicants' response, the following apply:

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-10 and 13-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record.

1. In claims 1-10 and newly added claims 13-17, recitation of "in vivo hydrolysable ester" is deemed as indefinite as esters or carbamates in general and as noted in specification, page 6, are compounds, which undergo in vivo hydrolysis. In that sense recitation of "in vivo hydrolysable esters" is not ambiguous and is acceptable. However, the definition of various substituent groups R^1 , R^2 , R^3 , R^4 include such groups, namely esters, alkoxycarbonyl, carbamates etc. which are also in vivo hydrolysable and therefore it is not clear what is the difference between these variable groups and the "in vivo hydrolysable ester" groups and therefore renders these claim ambiguous. Also note removal of protecting groups in claim 9 is also indefinite, as it is not clear what are these protective groups and how they differ from the above said groups.

Note this rejection is same as made in the previous office action except that the cancelled claims 11-12 are omitted and newly added claims are included in this rejection.

Applicants' traversal to overcome this rejection is not persuasive.

Contrary to applicants' urging that there is no ambiguity between ester groups embraced as substituents and the ester group included as "in vivo hydrolysable ester group", there is no evidence or guidance provided how would one distinguish one over other and what is the difference between the two. Applicants have not shown that one trained in the art would merely looking at the formula of claim 1 would be able to know which is an hydrolysable ester group and which is not as to ascertain which is a prodrug and which is not.

Hence, this rejection is proper and is maintained.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating cancer does not reasonably provide enablement for any or all for all diseases/disorders embraced in the claim language The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims for reasons of record.

The method claims 13-16 is drawn to "a method of producing anti-cancer effect, a method of producing ant-proliferative effect, a method of producing a CDK2 inhibitory, and a method of treating a disease or medical condition mediated by CDK2, based on the mode of action recited in the specification. The scope of the claim includes not only any or all conditions but also those condition yet to be discovered as mediated by cyclin activity for which there is no enabling disclosure. In addition, the scope of these claims includes treatment of various diseases, which is not adequately enabled solely based on the cyclin inhibitory activity of the compounds provided in the specification at pages 29-30. The instant compounds are disclosed to have cyclin inhibitory activity and it is recited that the instant compounds are therefore useful in treating any or all diseases where cyclin activity is implicated, for which applicants provide no competent evidence. Furthermore, the applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended host. Moreover many if not most of diseases such as autoimmune diseases, atherosclerosis are very difficult to treat and at present there is no known drug, which can successfully reverse the course of these diseases, despite the fact that there are many drugs, which can be used for "inflammatory condition". Note even a recent reference, Donnellan et al., FASEB Journal, 13, 773-777, 1999, suggest use of cyclin inhibitors at best for improving prognosis in cancer patients. See page 777, conclusion. That a single class of compounds can be used to treat all diseases embraced in the claims is an incredible finding for which applicants have not provided supporting evidence. Note substantiation of utility and its scope is required

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when utility is "speculative", "sufficiently unusual" or not provided. See *Ex parte Jovanovics*, 211 USPQ 907, 909; *In re Langer* 183 USPQ 288. Also note *Hoffman v. Klaus* 9 USPQ 2d 1657 and *Ex parte Powers* 220 USPQ 925 regarding type of testing needed to support in vivo uses. Next, applicant's attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 64 FR 71427 and 71440 (December 21, 1999) wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed method treating solely based on the inhibitory activity disclosed for the compounds. The state of the art is indicative of the requirement for undue experimentation.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use of the compounds in treating diseases that require cyclin inhibitory activity. 2) The state of the prior art: A very recent publication expressed that treating disease by cyclin inhibitory activity is still exploratory. 3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for r treating any or all condition of the instant compounds. Pharmacological activity

in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: Specification has no working examples to show treating any or all condition and the state of the art is that the effects of cyclin inhibitory activity are unpredictable and at best limited to cancer.

6) The breadth of the claims: The instant claims embrace any or all condition including those yet to be related to cyclin activity.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of receptor-ligand interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards treating the variety of diseases of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

This rejection is same as made in the previous office action over use claims 11 and 12 now rewritten as method of use claims. Applicants' argument to overcome this rejection is not persuasive for reasons of record. As for applicants' traversal, citing several US Patents, the following apply:

1. First of all, applicants should note that each case is examined for its own merits fro enablement and what is known in the prior art related the same subject matter.
2. Prior art search as noted in the rejection does not lend support for the scope of the instant method claims.
3. Applicants have not provided any reference or show passage in specification for to support the scope of the instant claims.
4. As for applicants' comments regarding training material example, XYZ, it is not a proper comparison. Examiner had provided a reference related to instant cyclin dependent kinase and that reference does not provide support for any or all diseases.

Hence , this rejection is deemed as proper and is maintained.

Information Disclosure Statement

References cited in the Information Disclosure Statements (paper # 6,7,9,10) are made of record.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP

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§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (703) 305-1674. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Supervisory Patent Examiner (SPE) of the art unit 1624 is Mukund Shah whose telephone number is (703) 308-4716. The fax phone number for the organization where this application or proceeding is assigned (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.


Venkataraman Balasubramanian

1/9/2004